



VarSeq as a Clinical NGS Platform

varSEQ

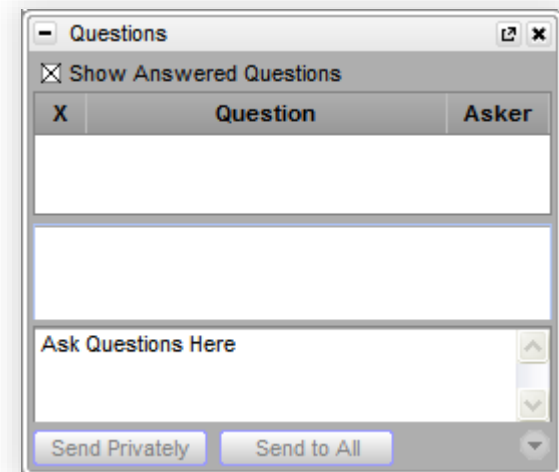
April 15, 2015

Gabe Rudy
VP Product & Engineering



Questions during the presentation

Use the Questions pane in your GoToWebinar window





1 VarSeq and Clinical NGS Background

2 Workflows: What is it Capturing and How?

3 Knowledge Capture: Leveraging Insights

4 Prioritize: Best Candidates First



Introducing VarSeq:
*Variant Discovery & Gene
Panels Made Easy*

varSEQ™

Gabe Rudy
VP of Product Development
October 1, 2014

GOLDEN HELIX
Accelerating the Quest for Significance™

- **Golden Helix founded in 1998**
- **Work on VarSeq revealed in 2013**
- **VarSeq built on mature technology**
- **6 months since launch:**
 - Build out features to support clinical labs
 - Responsive to feedback

Stakeholders



- Jason Byars
- David Gokhale
- Kelly Eggleton
- Bruno Ping
- Cristian Ionescu-Zanetti
- Reece Hart
- Ken Kaufman
- Sam Strom
- Jeff Moore
- Jeff Rosenfeld
- Scott Ness



UNM



Liverpool Women's
NHS Foundation Trust



FLUXION



Health

Royal Surrey County Hospital 

NHS Foundation Trust



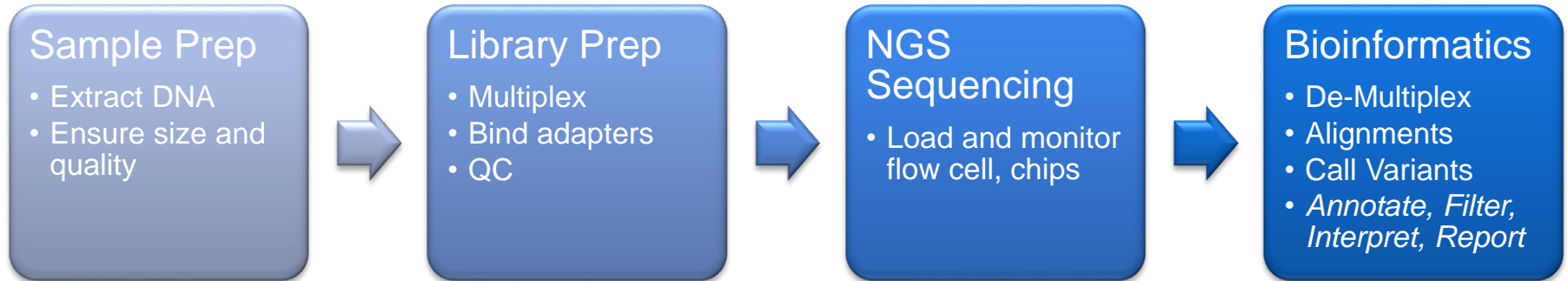
Cincinnati
Children's®



ILLINOIS

UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN

Laboratory Developed Tests



Applications

- Carrier Screening
 - CFTR, Prenatal/Preconception
- Hereditary
 - Cancer risk, Cardiomyopathy
- Pediatric/Diagnostic
 - Noonan Syn, Neuropathy, Epilepsy
- Cancer Gene Panels

Economics

- Panels cheaper than single-gene tests
- Minimal hardware requirements
- Many off-the-shelf kits for popular tests
- Vender supported workflows
- *With correct interpretation workflow, can efficiently handle reporting/sign-off*

File Tools Help

Import Export ?

Cancer Panel Workflow (2 Variants) Cancer Panel Workflow (2 Gene Names) Cancer Panel Workflow

E107279-058b03-12-L7555

Variant Sites Annot... Summary of COSMIC Mutations Left Aligned 71, GHI

Chr:Pos	Ref/Alt	Gene Names	Alt Allele Freq	In COSMIC?	Mutation ID (Unique)	Mutation CDS (U...	Mutation AA (U...
2:209113192	G/A	IDH1	0.0395792	True	1741220	c.315C>T	p.G105G
3:178927410	A/G	PIK3CA	0.0600601	True	328028	c.1173A>G	p.I391M

Read Depths (DP) (Current) 1,504

Less than 1,500 181

Equal to 1,500 0

Greater than 1,500 1,504

Missing 0

Alt Allele Freq (Current) 0.01 0.3

Less than 0.01 1,492

Equal to 0.01 0

Between 0.01 and 0.3 5

Equal to 0.3 0

In COSMIC? True 2

False 3

Missing 0

Detail GenomeBrowse

History

Sample Fields Table

Samples	Genotypes	Genotype Qualities (GQ)	Alt Allele Freq
E107279-058b03-12-L7555	A_G	99	0.0600601

Annotate Transcripts

Gene Names PIK3CA

Summary of COSMIC Mutations

In COSMIC?	True
Mutation ID (Unique)	328028
Mutation CDS (Unique)	c.1173A>G
Mutation AA (Unique)	p.I391M

Variant+Transcript Interactions

Transcript Name	Sequence Ontology	Transcript ID	Transcript Description	Transcript Type
1 NM_006218.2	missense_variant	NM_006218.2:c.1173A>G	NP_006209.2:p.Ile391Met	Missense

Workflows

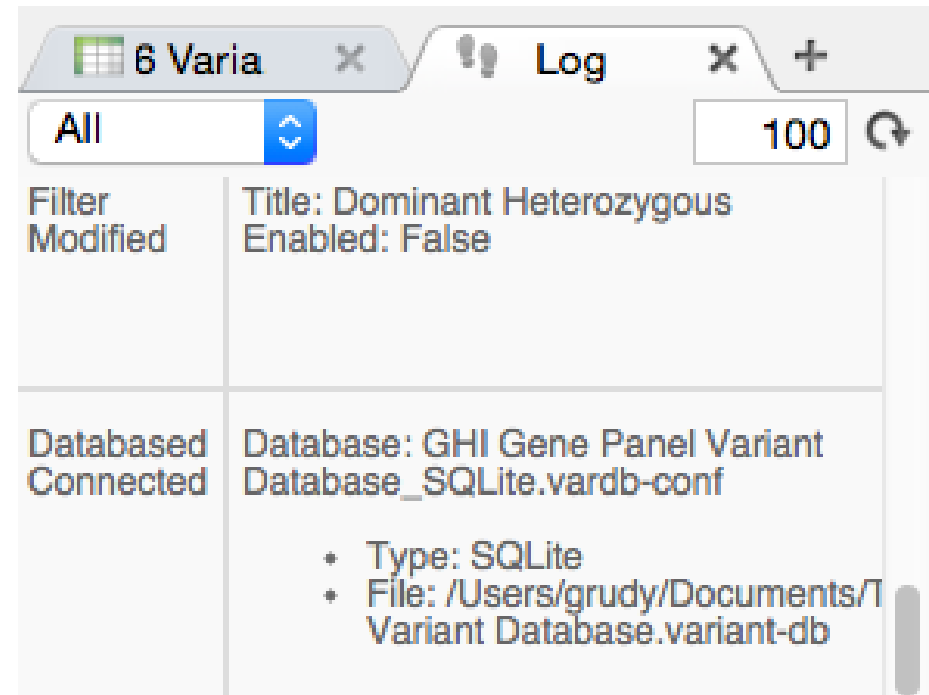
- Import Settings
- Choices of added annotations and algorithms
- Filters
- Table views of import and annotated data

Point (3: 106,726,375, 0.9625) 3 20 bp

Workflows: What is it Capturing and How?



- Every project can be saved as a template
- Create New Projects with a template to reproduce with new data
- Everything logged, with precise details of what happened, by whom and when.





[Demonstration]



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Knowledge Capture - Project Notes



- Rich text edit controls
- Save as HTML, PDF
- Grab content from:
 - Details view
 - Table
 - GenomeBrowse view
- Saved with project
- Multiple per project

The screenshot shows a web browser window with the following content:

- Browser tabs: Hereditary Panel Filter, Notes for Sample 093209, Log
- Address bar: Arial, 9, B, I, U
- Page title: Notes for Sample 093209
- Text: Test: Neuropathology panel
- Text: Results: Positive for REEP1 autosomal dominant pathogenic mutation.
- Table 1: Genotype and Read Depth data

Samples	Genotypes	Read Depths (DP)	Alt Allele Freq
093209	G_T	428	0.53271

- Table 2: Clinical Significance and Disease Name

Accession	Clinical Significance	Disease Name
1 RCV000001939.1	Pathogenic	Spastic paraplegia 31, autosomal dominant

- Text: [2:86509339 - G/T](#) - Coverage over 428 and clean alignment evidence:
- GenomeBrowse visualization showing a chromosome segment with a red vertical line indicating the mutation site.
- Read Depth plot for S5_NGS5_093209_SC_Sorted, showing a peak at the mutation site.
- Pile-up visualization showing individual sequencing reads aligned to the reference sequence.

Knowledge Capture – Variant Database



- Customizable set of fields and defaults
- Use for annotation
- Backends:
 - Single file (SQLite)
 - MySQL
 - PostgreSQL
- Fully logged
- Reversible
- Auto-fields:
 - Sample
 - Project

Hereditary Gene Panel Workflow | Neuropathy Gene Panel Assessments

Clear All

Chr X: 70443780 - C/T (Existing Record)

Sample: L1103794

Phenotype: Spastic paraplegia

Classification: Pathogenic

Notes: Male is hemizygous for variant. Agree with ClinVar assesment of Pathogenic for CMTX1

Sign Off: Lab Directory Sign-Off

Recent Assessments Using Current Schema

Date	User	Sample	Phenotype	Classification	Notes	Sign Off
2015-04-07 09:25	rudy@goldenhelix.com	L1103794	Spastic paraplegia	Pathogenic	Male is hemizygous for variant. Agree with ClinVar	True



[Demonstration]



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Annotate, Filter and Rank



Trio Workflow x Log x GenomeBrowse x +

Proband (NA19240)

Trio Workflow 50,457

de Novo	Compound Heterozygous	Recessive Homozygous	X-Linked
Read Depths (DP) (Cu) 48,788	Read Depths (DP) (Cur) 48,788	Read Depths (DP) (Cu) 48,788	Read Depths (DP) (Cu) 48,788
All MAF (NHLBI ESP65) 13,194	Genotype Qualities (G) 48,310	Genotype Qualities (G) 48,310	Genotype Qualities (G) 48,310
Effect (Combined) 5,267	All MAF (NHLBI ESP65) 21,524	All MAF (NHLBI ESP65) 12,878	All MAF (NHLBI ESP65) 12,878
de Novo Candidate 66	Effect (Combined) 8,427	Effect (Combined) 5,133	Segment 78
Alt Allele Freq (Current) 13	Compound Het? (Current) 538	Recessive Inheritance 56	Zygoty (Current) 21
13	538	56	21

628



PhoRank – Phenotype Based Gene Ranking



- **Sorting and Ranking harmonized**
- **Enter phenotype terms using HPO**
- **Propagates terms through HPO and GO**
- **Ranks genes in dataset by known associations with terms**
- **Provides path back to input terms**

The screenshot shows the PhoRank software interface. At the top, there is a window title bar that says "(63 Genes) deNovo". Below the title bar is a toolbar with icons for "Add", "View", "Refresh", "Export", and "deNovo". The main area displays a table with the following data:

Group by Genes			
	Gene Names	Gene Rank	Gene Score
>	TCOF1	0.990753	0.000366334
	COL3A1	0.961691	0.000352534
	RAB3GAP2	0.997358	0.000382268
	ANKRD11	0.997358	0.000382268
	LIAS	0.992074	0.000367525
	ALMS1	0.961691	0.000352534
	ALG13	0.94716	0.000349223
	BRWD3	0.896962	0.000344522
	POLA1	0.873184	0.000195044



[Demonstration]



- **Enables repeatable processes**
- **Supports clinical lab requirements**
- **Gene panels, exomes**
- **Simple and intuitive interface**
- **Fast and responsive**
- **Simple licensing model**





Questions or more info:

- Email info@goldenhelix.com
- Request an evaluation of the software at www.goldenhelix.com





Questions?

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